REMARKS

The Office Action dated May 7, 2002 has been carefully reviewed. Claims 2, 4-15, 20-22 are presented for examination. Claims 2, 4-15, 20-22 are rejected. Claim 21 has been withdrawn from consideration.

The Examiner has omitted claim 16 from the list of pending claims. A careful review of the file history will show that claim 16 was never canceled during prosecution. In a Preliminary Amendment filed on December 12, 1999, applicant's attorney indicated that claims 1-16 and 20-21 would remain pending in this application. In the Preliminary Amendment filed on March 6, 2002, claims 2, 4-16 and 20-22 were listed as pending in this application. Claim 1 was canceled in an amendment filed on November 7, 2001 and replaced with claim 22. Claim 21 was withdrawn from consideration. Thus the claims pending in the instant application are 2, 4-16, 20 and 22.

By the present amendment claim 22 has been amended by limiting the range of the water-soluble acid in the composition to "35-95%". Support for this limitation is found on page 6, lines 24-35 wherein it is disclosed that the acid can be present in various ranges from 1 to 95%, 5-90%, 20-80%, 35-60% and 50-95% by weight. It is submitted that the disclosure in the specification is sufficient to support a range of 35-95% for the acid component.

Attached hereto is a marked-up version of the change made to the claim by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Claims 2, 4-15(16), 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Sousa Goucha Jorge (EP 0 689,844). The Examiner has stated that the '844 reference "teaches poorly water soluble active agent compositions comprising a cyclodextrin, a water soluble acid, and a water soluble organic polymer wherein the amounts of these ingredients are within the instant ranges". The Examiner cites as support for this conclusion the Abstract; page 2, lines 25-43; page 3, lines 4-14; example 7; and the claims of the '844 reference. A careful reading of the portions of the reference cited by the Examiner does not reveal any reference to a water soluble acid as being part of the reference composition. According to the Abstract in the reference, the invention "relates to pharmaceutical compositions useful in the treatment of cerebrovascular disorders, containing an inclusion complex of vinpocetine formed with any kind of cyclodextrin". There is no reference to the inclusion of a water-soluble acid in the complex in either the Abstract or any of the claims. The reference even fails to include any reference to a water soluble acid in the claims drawn to the process for preparing the inclusion complex, i.e. claims 6, 15 and amended claims 5 and 14 of the '844 reference.

Vinpocetine dissolves well in ethanol and 0.1N HCl (see page 2, line 43 of '844). In Examples 2-5 of the reference, a method is disclosed for preparing the claimed complex. Although small amounts of HCl and tartaric acid are employed in the

preparation, it is clear from Example 2 that acid is not required to be present in the final complex since the solution was neutralized with 0.1N NaOH prior to drying at 70°C. The resulting complex contained 12.2% by weight of vinpocetine and a molar ratio of vinpocetine to ß-cyclodextrin = 1:2.2.

Applicant's claimed invention relates to a pharmaceutical composition comprising a sparingly water-soluble drug compound, a cyclodextrin, an acid and a water-soluble organic polymer. The four components are required in the composition in order to obtain the complementary effects at the microscopic level during dissolution of the composition (*See* page 3, lines 9-11 of the specification). As a result, the drug compound is made readily bioavailable to the organism to which it is to be administered (*See* page 3, lines 16-17 of the specification). The acid in the composition on exposure to water generates a low pH environment in which the solubility of the drug is increased. The acidic microenvironment is capable of complexing the solubilized drug causing the production of a supersaturated solution of the drug compound. The supersaturated solution is stabilized by the viscosity enhancing effects of the organic polymer which hinders precipitation of the drug as the pH increases, as the microenvironment becomes more dilute and as more water enters (*See* specification at page 15, lines 25-34).

Applicant's attorney wishes to direct the Examiner's attention to Table 1, page 20 of the specification which shows the dissolution profile of (-)-[2S-[2a,4a(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one from a composition of the present invention and from a conventional dosage form. In the conventional dosage form, the active ingredient is loaded on the sugar particles (*See* specification at page 20, line 14). As can be seen from the tabulated results, the drug compound is much more readily bioavailable from the claimed composition when compared to the conventional dosage form.

Example 7 on pages 23-24 of the instant specification describes the dissolution of methylene blue from a composition of the present invention in test media having pH values ranging from 1.55 to 7.0 (*See* specification at page 23, lines 28-29). As can be seen from the tabulated results on page 24, methylene blue is completely released from the composition within 45 minutes irrespective of the pH.

Example 8 on pages 24-27 of the instant specification illustrates the favorable dissolution profile of several compositions of the present invention. From the data summarized in Tables 5-10 (pages 25-27) it can be concluded that at 45 minutes at least 95% of the drug compound is released. In each of the Examples the compositions contained a water soluble acid as a component.

These examples clearly illustrate the favorable dissolution profile of the compositions of the present invention. The compositions of th present invention are characterized by a fast release of the incorporated active ingredient. The acid, drug compound, cyclodextrin and organic polymer are intimately mixed together. This intimate

admixture is important since the effects of the components are complimentary at the microscopic level during dissolution of the compositions (*See* specification at page 3, lines 5-11).

EP 0 689,844 relates to an inclusion complex of vinpocetine which is formed with a cyclodextrin. The inclusion complex is preferably dispersed in a polymer matrix that provides modified, i.e, extended, release of the active agent. Although the compositions of the reference may contain a limited amount of acid, the acid is used to prepare the vinpocetine-cyclodextrin complexes. As indicated above, the acid is not an integral part of the '844 compositions since the acid used to prepare the vinpocetine-cyclodextrin complex may be neutralized with NaOH prior to isolating the finished complex. Applicants submit that the claims as amended contain an amount of water soluble acid far in excess of any residual acid that may remain in the vinpocetine complexes of the cited reference.

With regard to the release profile, the Examiner has pointed out that in the '844 patent a release profile for Example 7 in water at 37°C is provided and shows that at 60 minutes, between 48.4% and 32.7% of the drug is released depending upon the amount of Methocel K4MP present. According to the Examiner, less drug is released with increasing amounts of Methocel. The Examiner then concludes that it would have been obvious to one skilled in the art to decrease the amount of Methocel in order to increase the dissolution of the composition, thus providing "a faster release composition of the [drug] agent". It is submitted that decreasing the amount of polymer present results in only a minimal increase in the dissolution rate.

In Example 6 of the reference the dissolution properties of tablets containing vinpocetine (Tablet A) and tablets containing vinpocetine in the form of an HP-ß-cyclodextrin complex (Tablet B) were compared. at 37°C in 1000 ml of water. Tablet A contains microcrystalline cellulose while there is no organic polymer in Tablet B. However, Tablet B contains in addition croscarmellose sodium which is a generally accepted tablet disintegrating agent. It is well known in the art that tablet disintegration accelerates the release rate. The data set forth in Table II, however, show that the release rate from the tablet is not high, particularly in Tablet B which contains the tablet disintegrating agent. After 60 minutes only 72% (7.16 mg) of the active ingredient is released. After 120 minutes, only about 90% (8.98 mg) is released. In Tablet A after 60 minutes, only 16% of the active ingredient is released and only 26% is released after 60 minutes. In Example 7, tartaric acid and Methocel K4MP are added to the composition. The addition of an organic polymer to the composition (minus the tablet disintegrating agent) retards the release of vinpocetine even further as can be seen from the results set forth in Table III, since the release rate is higher in the compositions which do not contain Methocel K4MP

The compositions of the present invention have a favorable, i.e. fast, dissolution profile. Claim 22 requires that at 5, 15 and 45 minutes after addition of quantity of the composition containing 100 mg of the drug compound to 600 mL of 0.1N hydrochloric acid at 37°C, from 7 to 25 %, 45 to 70 % and at least 96 % respectively of the drug

compound is in solution in said hydrochloric acid. That is, after 45 minutes, at least 96 % of the drug compound is in solution in said hydrochloric acid.

Moreover, from the results set forth in Table 4 on page 24 of the instant application, it is clear that the release profile of the present compositions is independent of the pH of the release medium. In a neutral, aqueous release medium, the compositions are also characterized by a fast release, a release which is faster than the one reported in the cited reference (Example 6) despite the presence of an organic polymer, i.e. Methocel E5, in the present compositions.

The Examiner has stated that the '844 reference "also teaches that the polymer is rate controlling and extends the release of the formulation" and concludes that it would be obvious to one skilled in the art to decrease the amount of Methocel in order to increase the dissolution of the composition to provide a faster release composition of the active ingredient. As shown in Example 6 of the reference and as described above, decreasing the % of Methocel only results in a modest increase in the dissolution after 120 minutes. Applicant has not merely decreased the amount of Methocel in order to increase the dissolution of the claimed composition. Rather, applicants' claimed invention requires that the pharmaceutical composition comprise specified percentages of a sparingly water-soluble drug compound, a cyclodextrin, a water-soluble acid and a water-soluble organic polymer which provides a fast drug dissolution profile and favorable bioavailability of the drug compound from the composition.

Thus, from the above it can be concluded that a skilled person could not derive the present invention from the disclosure in EP 0,689,844. That is, the disclosure of the '844 reference would not motivate one of ordinary skill in the art to make the claimed composition comprising specified percentages of a sparingly water-soluble drug compound, a cyclodextrin, a water-soluble acid and a water-soluble organic polymer having a specified drug dissolution profile as required by the instant claims. Said reference does not disclose the need of a substantial amount of acid in order to arrive at a composition with a faster drug dissolution profile. As indicated above, the amount of acid present in applicant's composition is high enough to provide a highly acidic microenvironment when brought in contact with water. This highly acidic environment results in an increased solubility of the drug compound. In addition, the cited reference would not motivate the skilled artisan to incorporate a substantial amount of an acid as an essential component of the composition since '844 discloses that the acid may be neutralized in the final composition by the addition of base. It is submitted, therefore, that applicant's claimed compositions are not obvious over the disclosure in De Sousa Goucha Jorge.

Reconsideration of the rejection of claims 1, 2, 4-15[16] and 20 and 22 under 35 U.S.C. 103(a) as being unpatentable over EP 0 689,844 is courteously requested.

In view of the above discussion and the amendments herein being made to the claims, it is believed that all of the outstanding objections and rejections have been removed. Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted

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IN THE CLAIMS

22 (twice amended). A solid pharmaceutical composition comprising by weight 0.001 to 50 % of a sparingly water-soluble drug compound, 5 to 70 % of a cyclodextrin, [1] 35 to 95 % of a physiologically tolerable water-soluble acid, and 0.05 to 35 % of a physiologically tolerable water-soluble organic polymer characterized in that at 5, 15 and 45 minutes after addition of a quantity of the composition containing 100 mg of drug to 600 ml of 0.1 N HCl at 37 °C from 7 to 25 %, from 45 to 70 % and at least 96 % of drug is in solution; [in said hydrochloric acid, wherein said physical state of said composition is a glass thermoplastic phase].